[0254] Still another aspect of the present invention relates to methods for generating non-human animals and stem cells having a functionally disrupted endogenous gene. In a preferred embodiment, the method comprises the steps of:

[0255] (i) constructing a transgene construct including (a) a recombination region having at least a portion of an IBD gene, which recombination region directs recombination of the transgene with the gene, and (b) a marker sequence which provides a detectable signal for identifying the presence of the transgene in a cell;

[0256] (ii) transfering the transgene into stem cells of a non-human animal;

[0257] (iii) selecting stem cells having a correctly targeted homologous recombination between the transgene and the gene;

[0258] (iv) transfering cells identified in step (iii) into a non-human blastocyst and implanting the resulting chimeric blastocyst into a non-human female; and

[0259] (v) collecting offspring harboring an endogenous gene allele having the correctly targeted recombination.

[0260] Yet another aspect of the invention provides a method for evaluating the potential of an agent to cause an IBD or to protect against development of an IBD by (i) contacting a transgenic animal of the present invention with a test agent, and (ii) ascertaining the presence, and more preferably the level, of onset or degree of severity of an inflammatory bowel disease or disorder, and comparing that with an untreated transgenic animal or transgenic animal treated with a control agent.

[0261] X. Exemplification

[0262] The following Table 1 teaches genes whose up-regulation or down-regulation, as indicated by "↑" and "↓", respectively, has been found to be associated with UC and CD. The genes are grouped according to their general functionality, as follows,

[0263] I Chemokines+cytokines and growth factors

[0264] II Inflammatory mediators

[0265] III Cell cycle regulators/transcription factors

[0266] IV Cancer Related

[0267] V HLA or immune function genes

[0268] VI Antimicrobial

[0269] VII ECM and remodelling

[0270] VIII Others: Carbohydrate metabolism, Fatty acid metabolism, Protein folding/modification/degradation

TABLE 1

| | UC | CD | Acc No. | Gene Names | Chromosome | Microsatellite Markers |
|---|---|---|---|---|---|---|
| I | ↑21.4 | ↑12.8 | Y00787 | MDNCF/IL-8 | 4q13–q21 | D4S392-D4S2947 |
| I | ↑15.3 | | X54489 | MGSA (GRO1) | 4q21 | D4S400-D4S1534 |
| I | ↑7.9 | | M57731 | MIP-2 (GRO2) | 4q21 | D4S392-D4S2947 |
| I | ↑8.9 | ↑4.1 | M28130 | IL8 | 4q13–q21 | D4S392-D4S2947 |
| I | ↑6.8 | ↑3.9 | X57351 | IP-10 | 11 | pTEL-D11S1318 |
| I | ↑6 | | J04130 | MIP-1 /SCYA4 | 17q21 | D17S933-D17S800 |
| I | ↑3.4 | | X53800 | MIP-2 (GRO3) | 4q21 | D4S400-D4S1534 |
| I | ↑3.2 | | M69203 | MIP-1 /SCYA2 | 17q21 | D17S933-D17S800 |
| I | ↑4.6 | | X04500 | pro-IL-1 | 2q14 | D2S293-D2S121 |
| I | ↑3.5 | | X53296 | IL-1RA | 2q14 | D2S293-D2S121 |
| I | ↑3.3 | | X04602 | IL-6 | 7q21 | D7S829-D7S673 |
| I | ↑3 | | J03756 | Growth hormone 2 (GH2) | 17q22–q24 | D17S794-D17S795 |
| I | ↓3.5 | | D16431 | Hepatoma-derived growth factor (HDGF) | 17q2–q24 | D17S794-D17S795 |
| I | | ↓4 | M58286 | TNF Receptor member 1A | 12p13.2 | D12S99-D12S358 |
| II | ↑35.5 | | S75256 | Neutrophil lipocalin (HNL) | — | — |
| II | ↑10.4 | | X99133 | Neutrophil gelatinase-associated lipocalin (NGAL) | 9q34 | D9S1821-D9S159 |
| II | ↑8.7 | | X85781 | Nitric oxide synthase (NOS2) | | — |
| II | ↑5.1 | | X65965 | Mitochondrial superoxide dismutase (SOD2) | 6q25.3 | D6S442-D6S1581 |
| II | ↑5.5 | ↑4.6 | M44230 | Phospholipase A2, group IIA (PLA2G2A) | 1p35 | — |
| II | ↑5.3 | | X51441 | Serum amyloid A (SAA) | 11p | — |
| II | ↑3.9 | | J03474 | Serum amyloid A (SAA3) | 11p15.1 | D11S921-D11S1369 |

**EXHIBIT B**

TABLE 1-continued

| | UC | CD | Acc No. | Gene Names | Chromosome | Microsatellite Markers |
|---|---|---|---|---|---|---|
| V | ↓3 | ↓6 | M84526 | Complement factor D (DF) | — | pTEL-D19S413 |
| V | ↓3.9 | | M38690 | CD9 antigen | 12p13 | D12S99-D12S358 |
| V | ↑5 | | M28590 | MHC Dg | 6 | |
| VI | ↑20.4 | ↑40.8 | M97925 | Defensin 5 (DEFA5) | 8pter–p21 | D8S552-D8S549 |
| VI | ↑6.8 | ↑7.7 | U33317 | Defensin 6 (DEFA6) | 8pter–p21 | D8S277-D8S550 |
| VII | ↑16.2 | ↑3.3 | L23808 | MMP-12 (Macrophage elastase) | 11q22.2–q22.3 | D11S1339-D11S1343 |
| VII | ↑6.4 | | J05070 | MMP-9 (Gelatinase B) | 20q11.2–q13.1 | D20S119-D20S197 |
| VII | ↑4.7 | | X54925 | MMP-1 (Interstitial collagenase) | 11q22.3 D11S1343-→ | D11S1339- |
| VII | ↑4.2 | | X05232 | MMP-3 (Stromelysin 1) | 11q22.3 | D11S1339-D11S1343 |
| VII | ↑13.3 | ↑3.8 | L10343 | Elastase specific inhibitor (Elafin) | 20q12–q13 | D20S119-D20S197 |
| VII | ↑11 | ↑3.1 | Z74616 | COL1A2 | 2q37 | D2S2158-D2S125 |
| VII | ↑7.3 | | X52022 | COL6A3 | 2q37 | D2S2158-D2S125 |
| VII | ↑6.9 | ↑3.6 | M55998 | COL1A1 | 17q21.3–q22 | D17S791-D17S794 |
| VII | ↑4.8 | | X06700 | COL3A1 | 2q31 | D2S2257-D2S115 |
| VII | ↑4.7 | | X15882 | COL6A2 | 21q22.3 | — |
| VII | ↑3.9 | | X05610 | COL4A2 | 13q34 | D13S285-qTEL |
| VII | ↑3.7 | ↑3.3 | HG2157-HT2227 | Mucin 4 (MUC4) | 3q29 | — |
| VII | ↑3.1 | | X52003 | Trefoil factor 1 (TFF1) | 21q22.3 | D21S1259-qTEL |
| VII | | ↑4.6 | M22406 | Intestinal mucin | — | — |
| VII | ↑6.4 | | J03040 | Osteonectin (SPARC) | 5q31.3–q32 | D5S436-D5S470 |
| VII | ↑4 | ↑3.2 | X17042 | Proteoglycan 1 (PRG1) | 10q22.1 | D10S210-D10S537 |
| VII | ↑3.9 | | D11428 | Peripheral myelin protein 22 (PMP22) | 17p12–p11.2 | D17S804-D17S799 |
| VII | ↑3.8 | | X02761 | Fibronectin 1 (FN1) | 2q34 | D2S137-D2S164 |
| VII | ↑3.7 | | M77349 | Transforming growth factor beta-induced (TGF f) | 5q31 | D5S393-D5S500 |
| VII | ↑3.2 | | D13666 | Osteoblast specific factor 2 (OSF-2) | 13 | D13S267-D13S1253 |
| VII | ↑3.1 | | M10321 | von Willebrand factor | 12p13.3 | D12S99-D12S358 |
| VII | ↑3 | | L09190 | Trichohyalin (THH) | 1q21–q23 | D1S439-D1S459 |
| VII | | ↑3.1 | D88422 | Cystatin A (CSTA) | 3q21 | — |
| VII | | ↑4.7 | X58199 | Adducin 2 (ADD2) | 2p13–p14 | — |
| VII | | ↑3.7 | M86933 | Amelogenin (AMELY) | Yp11.2 | — |
| VII | | ↓3.2 | D45370 | Adipose specific collagen-like 2 (APM2) | 10 | D10S1786-D10S541 |
| VII | | ↓3.8 | X73501 | Cytokeratin 20 | — | — |
| VII | ↓4 | | U60061 | Zygin 2 | 2 | D2S367-D2S2230 :D2S177-D2S119 |
| VII | ↓(↑)3 | | AF006087 | Actin-related complex | 3 | D3S3591-D3S1283 |
| VII | ↓(↑)6 | | D87460 | Paralemmin | 19p13.3 | pTEL-D19S413 |
| VIII | ↑50.5 | | D26416 | Esterase D (ESD) | 13q14.1–q14.2 | D13S328-D13S168 |
| VIII | ↑4.7 | | M15656 | Aldolase B | 9q21.3–q22.2 | D15S202-D15S157 |

TABLE 1-continued

| | UC | CD | Acc No. | Gene Names | Chromosome | Microsatellite Markers |
|---|---|---|---|---|---|---|
| VIII | | ↑6.3 | J04040 | Glucagon (GCG) | 2q36–q37 | D2S156-D2S376 |
| VIII | | ↓4.4 | L31801 | Monocarboxylate transporter 1 (MCT1) | 1p13.2–p12 | D1S418-D1S514 |
| VIII | ↓3 | | D10523 | Oxoglutarate dehydrogenase (OGDH) | 7p14–p13 | D7S521-D7S478 |
| VIII | ↓4 | | M12963 | Alcohol dehydrogenase 1a (ADH1) | 4q21–q23 | — |
| VIII | ↓4.5 | | Y00339 | Carbonic anhydrase II (CA2) | 8q22 | D8S275-D8S273 |
| VIII | ↓4.9 | ↓3.1 | L10955 | Carbonic anhydrase IV (CA4) | 17q23 | — |
| VIII | ↓12.7 | ↓3.1 | L05144 | Phophoenolpyruvate carboxykinase 1, soluble (PCK1) | 20q13.31 | D20S183-D20S173 |
| VIII | ↑3 | | U07158 | Syntaxin 4A (STX4A) | — | — |
| VIII | ↑3 | | L27706 | Chaperonin subunit 6A (CCT6A) | 7 | D7S530-D7S509 |
| VIII | ↓7 | ↓3.1 | J04093 | UDP-glycosyl-transferase 1 (UGT1) | 2 | D2S2158-D2S125 |
| VIII | ↓3.2 | | U20499 | Sulfotransferase family 1A (SULT1A3) | 16p11.2 | — |
| VIII | ↓3 | | M15182 | -glucuronidase (GUSB) | 7q21.11 | — |
| VIII | ↓4 | | U08854 | UDP glucuronosyltrans-ferase precursor (UGT2B15) | 4q13 | D4S1619-D4S392 |
| VIII | ↓5 | | D87292 | Thiosulfate sulfurtransferase (TST) | 22 | D22S277-D22S283 |
| VIII | ↓13 | ↓4 | M22324 | Aminopeptidase N/CD13 (ANPEP) | 15q25–q26 | D15S202-D15S157 |
| VIII | ↓12 | ↓7 | M22960 | Protective protein for b-galactosidase (PPGB) | 20q13.1 | D20S119-D20S197 |
| VIII | ↑3.4 | | X90908 | Fatty acid binding protein 6 (FABP6) | 5q23–q35 | — |
| VIII | | ↑4.1 | J02874 | Fatty acid binding protein 4 (FABP4) | 8q21 | — |
| VIII | ↓3 | | M10050 | Fatty acid binding protein 1 (FABP1) | 11p15.5 | D11S1318-D11S909 |
| VIII | ↓3 | | L24774 | Mitochondrial d3, d2-CoA-isomerase | — | |
| VIII | ↓4 | | D16294 | Mitochondrial 3-oxoacyl-CoA thiolase (ACAA2) | 18 | D18S1118-D18S474 |
| VIII | ↓4 | | M77144 | 3 b-hydroxysteroid dehydrogenase (HSD3B2)) | 1p13.1 | D1S418-D1S514 |
| VIII | ↓5 | | D10511 | Mitochondrial acetoacetyl-CoA thiolase | — | — |
| VIII | ↓7 | | Z80345 | Acyl-Coenzyme A dehydrogenase (ACADS) | 12q22–qter | D12S366-D12S340 |
| VIII | ↓7 | | L11708 | 17 b-hydroxysteroid dehydrogenase II (HSD17B2) | 16q24.1–q24.2 | D16S515-D16S422 |